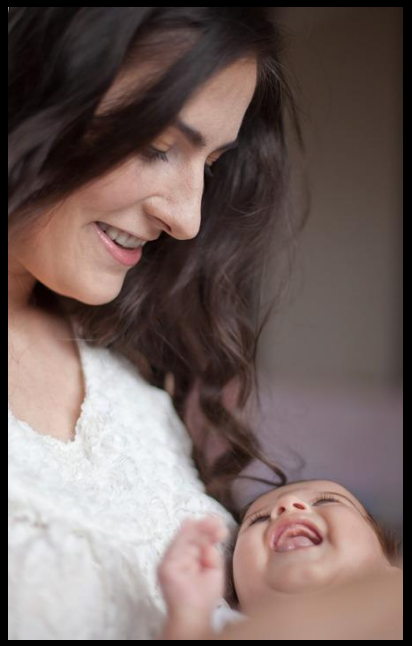
Understanding Opioid Dependence: a significant harm of long-term opioid therapy



Mark Sullivan, MD, PhD
University of Washington
Psychiatry and Behavioral Sciences
Anesthesiology and Pain Medicine
Bioethics and Humanities

UNIVERSITY of WASHINGTON

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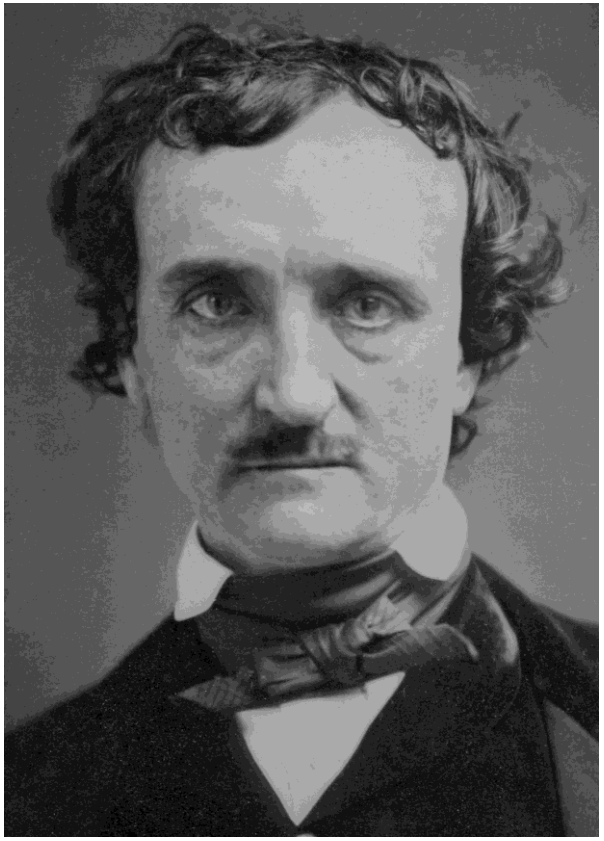


… with an utter depression of soul which I can compare to no earthly sensation more properly than to the after-dream of the reveller upon opium--the bitter lapse into everyday life--the hideous dropping off of the veil.
–Edgar Allen Poe, The Fall of the House of Usher

My thesis:

Prescription opioid policy is often framed as a balance of the right to pain relief vs the risk of addiction. For humans, physical survival depends on social survival, so our brains have evolved to make both physical and social injury painful, with our endogenous opioid system modulating both forms of pain to promote both forms of survival.

Long-term exog nedications disrupt this syst

Ms. B who has fibromyalgia

- 38 yr old married RN with 2 children, 8yr, 5yr
- MVA 3 years ago when she was rear-ended
- Initially she had whiplash, chronic neck pain which gradually spread down her spine and then her limbs and whole body
- Unable to work since her accident
- Spine MRI reveals only degen. disc disease
- She reports 10/10 pain despite oxycodone SR 80mg BID (240mg MED), asks for more

What do opioids do for Ms. B?

- Pain relief (Goldenberg 2016)
  - Opioids commonly used for FM (11-69%)
  - Opioids not diminished after FDA approval of duloxetine, pregabalin, milnacipran
  - Less effective than non-opioids in two prospective 1-2 yr. observational studies
  - Opioid use associated with: lower education, unemployment, disability, MH, SUD, suicide att.
  - Patients rate hydrocodone as the most helpful

What do opioids do for Ms. B?

- Addiction: DSM-V Opioid Use Disorder
  - Opioids are often taken in larger amounts or over a longer period of time than intended.
  - There is a persistent desire or unsuccessful efforts to cut down or control opioid use.
  - A great deal of time is spent in activities necessary to obtain the opioid, use the opioid, or recover from its effects.
  - Craving, or a strong desire to use opioids.

What do opioids do for Ms. B?

- DSM V OUD continued:
  - Recurrent opioid use resulting in failure to fulfill major role obligations at work, school or home.
  - Continued opioid use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of opioids.
  - Important social, occupational or recreational activities are given up or reduced because of opioid use.
  - Recurrent opioid use in situations in which it is physically hazardous
  - Continued use despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by opioids.

Rates of OUD in long-term opioid therapy (LtOT)patients

- Vowles review of 38 studies (2015)
  - Problematic use: <1% to 81%
  - Misuse 21% to 29%
  - Addiction 8% to 12%
- Boscarino study 705 LtOT patients (2015)
  - No DSM V OUD: 59% (0-1)
  - Mild 2-3 sxs.: 28%
  - Moderate 4-5 sxs.: 10%
  - Severe 6+ sxs.: 3.5%

Rates of OUD in long-term opioid therapy (LtOT)patients

- Von Korff: OUD in LtOT patients by PRISM after opioid dose and risk reduction initiative
  - 21.5% COT patients in the intervention clinics
  - 23.9% COT patients in the control clinics.

Rates of OUD in long-term opioid therapy (LtOT)patients

Von Korff PRISM5 interview data:

Table 2
Profile of DSM-5 symptoms for mild and moderate-severe cases of prescription opioid use disorder ascertained by the PRISM5 among chronic opioid therapy (COT) patients.

	Percent of mild cases (N = 278)	Percent of moderate-severe cases (N = 73)
Wanted to stop or cut down more than once or tried to cut down or stop more than once and was unable	88.1%	93.2%
Strong urge or desire to take opioids or preoccupied with use of opioids	44.7%	67.1%
Used more than intended or longer than planned	33.7%	58.3%
Felt sick a lot of the time from opioid use	5.1%	21.9%
Gave up or cut down important activities due to opioids	23.8%	74.0%
Continued opioid use despite emotional or physical problems due to opioids	8.8%	51.4%
Continued opioid use despite problems with others due to opioid use	2.2%	21.9%
Opioids interfered with job/school/home/family	13.5%	61.6%
Did dangerous activities more than once while using opioids	8.3%	32.9%
Tolerance (with excessive use)	21.9%	47.9%
Withdrawal (with excessive use)	12.1%	30.4%

What do opioids do for Ms. B?

- DSM V opioid dependence indicators:
  - *Tolerance, as defined by either of the following: (a) a need for markedly increased amounts of opioids to achieve intoxication or desired effect (b) markedly diminished effect with continued use of the same amount of an opioid
  - *Withdrawal, as manifested by either of the following: (a) the characteristic opioid withdrawal syndrome (b) the same (or a closely related) substance are taken to relieve or avoid withdrawal symptoms
    - These criteria not considered to be met for those individuals taking opioids solely under appropriate medical supervision.

Does Ms. B have opioid dependence?

- Not DSM IV opioid dependence
- Physiological vs psychological dependence
- "Complex persistent dependence" (Ballantyne 2012)
  - Arises during Rx long-term opioid therapy
  - Includes tolerance and withdrawal
  - Withdrawal: not only sweating, anxiety, insomnia, but also anhedonia, hyperalgesia
  - Aberrant behaviors typical of addiction may not be present due to regular opioid supply by Rx

Centralized pain: fibromyalgia

- Widespread pain but no abnormalities in painful muscles or joints
- Hypersensitivity to pressure, heat, cold, electricity, sound
- Adverse childhood experiences common, esp. physical and sexual abuse
- Classic example of functional pain syndrome, somatization, somatoform d/o
- "We can't find anything wrong with you"

FM like other functional pain synd.

- Similar syndromes:
  - Chronic fatigue, irritable bowel, interstitial cystitis
- Often includes other dysfunction with:
  - Sleep, mood, memory, concentration
- Effective treatments
  - Antidepressants, anticonvulsants, CBT, exercise
- Ineffective treatments
  - NSAIDs, surgery, local injections, opioids

Centralized and generalized pain: fibromyalgia

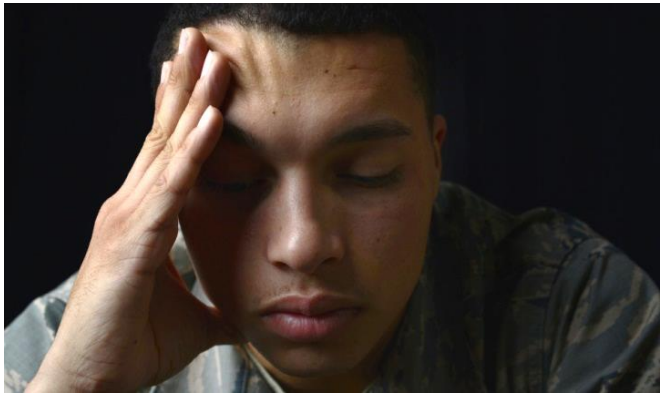
- Altered CNS nociceptive processing similar to IBS, IC, TMD, tension HA (Clauw 2014, 2015)
- Increased activation on fMRI: salience network, secondary somatosensory cortex… (Kutch 2017)
- Increased connectivity between insula and default mode network, proportional to pain
- Elevated substance P, NGF, glutamate in CSF
- Reduced conditioned pain modulation
- Endogenous opioid tone increased
  - More tonic, less phasic opioid release

Ms. B has been traumatized

- As part of her initial work-up at pain clinic, she scored 5/5 on PC-PTSD5 screener
  - She re-experiences her MVA in nightmares
  - She avoids driving in that part of town
  - She is easily startled, angered, w insomnia
  - She has withdrawn from colleagues, friends
  - She cannot stop blaming herself for the MVA
- She appears to have PTSD

Role of psychological trauma in chronic pain

- Prevalence of PTSD in US is 7.8%
- Chronic pain reported in 35-50% of PTSD pts.
- Among patients presenting for care of chronic pain, 7-50% meet PTSD criteria.
- Common chronic pain: pelvic pain, low back pain, facial pain, bladder pain, fibromyalgia



Role of PTSD in chronic pain

- PTSD: more intense pain, affective distress, disability
- PTSD: opioid therapy more likely, higher doses, multiple opioids, concurrent benzos, early refills, adverse events (Seal, 2012)
- PTSD: significant linear association with wide range of pain outcomes: pain intensity, activity interference, sleep, disability, global health, opioid risk (Langford, 2018)

Ms. B has earlier psych trauma

- As you work with Ms. B to address PTSD sxs. (prazosin), depression (duloxetine) and disability (PT, OT) she reveals that she was beaten by her first husband (age 20-23)
- She eventually left this husband, but had nightmares of beatings for years
- These had resolved about a decade before her MVA

Role of physical and psychological causes of pain may shift over time

- Prospective fMRI study of patients w LBP (Hashimi, 2013)
- LBP progresses- acute→ subacute→ chronic patterns of brain activation shift from sensory/nociceptive→emotion-related regions
- But as LBP shifts from somatogenic to psychogenic, *it feels the same to the patient*
- This LBP thus does not have a single cause or "neurological signature" (Wager)

Physical and social pain may share the same neurobiological structures

- Most prefer broken leg over broken heart, but medicine treats broken legs as more real
- Social rejection, exclusion, loss can be the most "painful" experiences of human life
- Physical injury and social rejection produce activation of same brain structures on fMRI: anterior cingulate, anterior insula
- Eisenberger: "social attachment system may have piggybacked onto opioid substrates of physical pain system to maintain proximity with others…"

Physical and social pain similarities

- Sensitivity to physical and social pain linked
  - Same people
  - Experiments show persons more sensitive to physical noxious stimuli also more sensitive to social rejection (Eisenberger 2006)
  - Same treatments
  - Physical and social pain respond to same meds
    - opioids relieve separation distress (Panksepp, 1978)
    - Acetaminophen reduces social and physical pain (Dewall, 2010)

Endogenous opioid system (EOS) throughout animal kingdom

- Invertebrates have no EOS
- Amphibians, reptiles, fishes have an EOS that modulates only physical injury pain
  - Suppresses pain if injured while fleeing predator
  - Rats forced to swim in ice water
  - Injured patients who do not feel pain until at ED
- Mammalian EOS also modulates the pain of physical injury, but…

Endogenous opioid system (EOS) throughout animal kingdom

- In mammals, opioids also serve to promote social bonds essential for survival.
- In non-primate mammals, most crucial bonds are with mates and offspring
  - Known to be supported by oxytocin system
  - But EOS supports these most basic bonds too
  - Rat pups w deficient EOS do not bond to mothers
  - EOS necessary for development of social play

Endogenous opioid system (EOS) throughout animal kingdom

- Primate EOS allows complex social networks
  - As social networks grow from rodents to primates benefits and conflicts increase
  - Endorphin release during primate grooming helps defuse these stresses and assure relationships available, but limited to group size of about 20

Endogenous opioid system (EOS) throughout animal kingdom

- Human social bonds more complex, extensive so need support beyond grooming (Dunbar):
  - Laughter "primitive chorusing vocalization"
  - Singing, dancing, drama, religious ceremonies
- Adult attachment style related to EOS
  - PET: avoidant attachment related to lower mu receptor availability in amygdala, ACC, insula, PFC
  - BPD, ASP show EOS dysregulation (Bandelow)

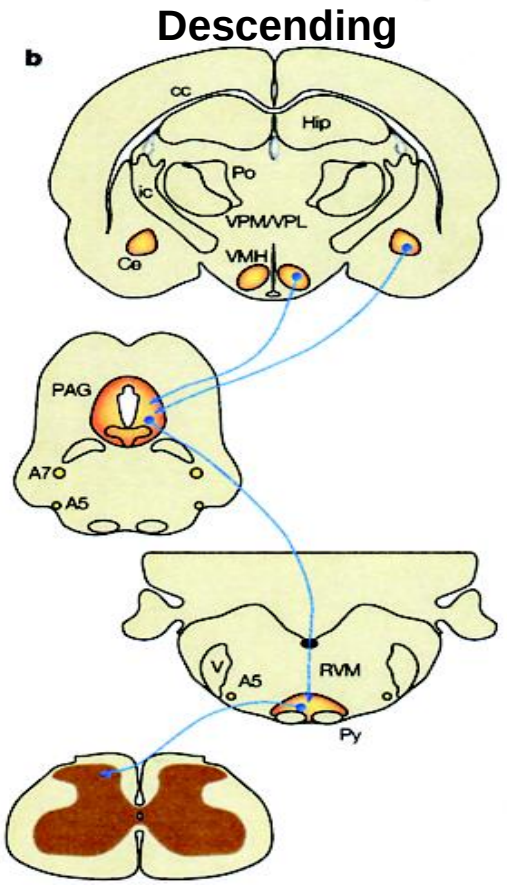
Endogenous opioid system (EOS) throughout animal kingdom

- In humans, social play supports social bonding and social, cognitive, emotional development
  - Adult social relationships → pain tolerance
  - fMRI: partner caress→ EOS → pain tolerance

Endogenous opioid system links chronic pain and major depression

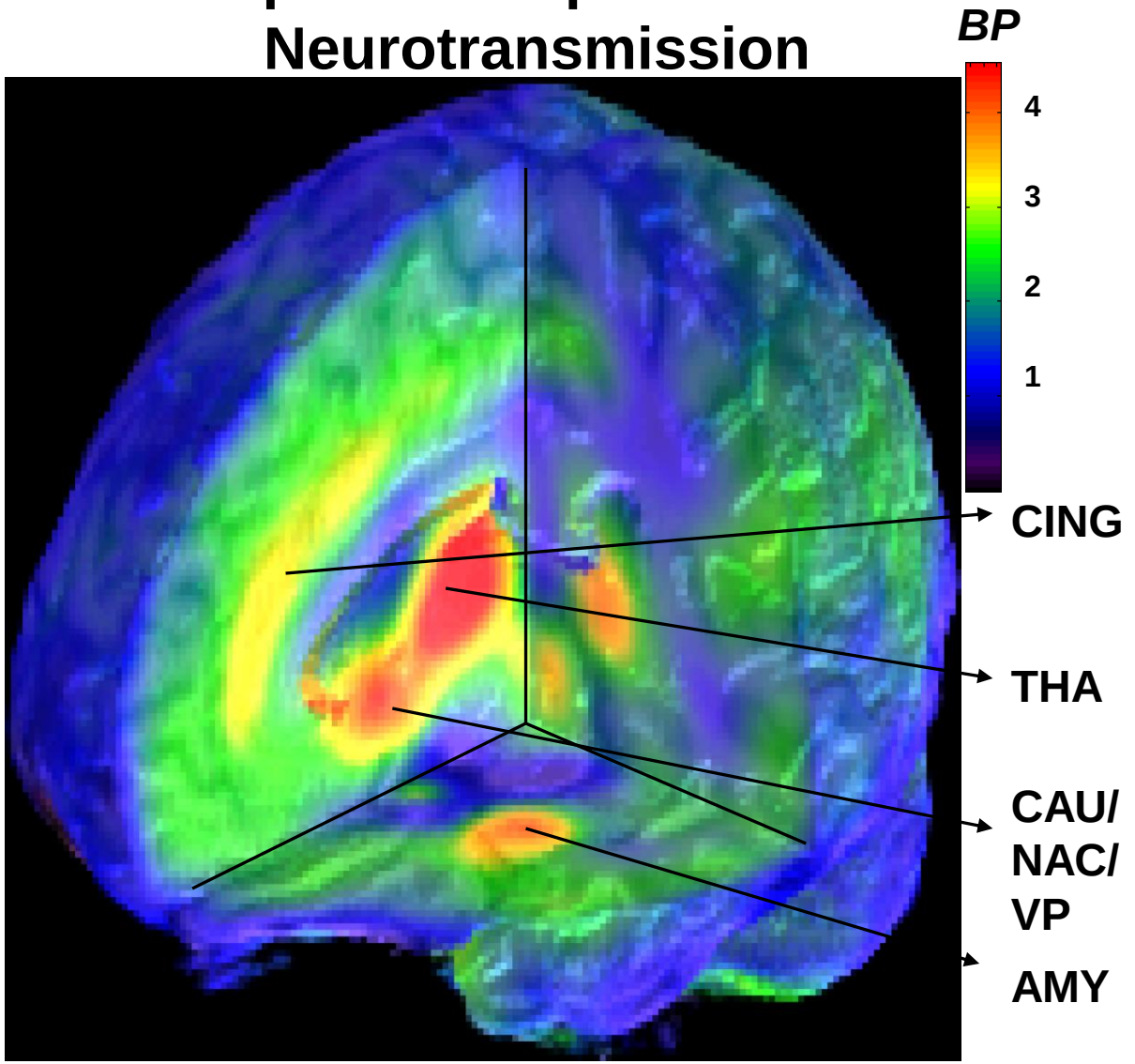
- Recent neuroimaging studies show many brain areas active during both pain and depression (ACC, insula, amygdala, and DLPFC) are laden with opioid receptors.
- Baliki and Apkarian have proposed that pain, anxiety and depression form a continuum of aversive behavioral learning, which enhances survival by protecting against threats.
- The transformation of nociception into behavior to promote survival is extended to incorporate negative moods.

CNS Inhibitory Controls



Distributed in pain regions but also "affective / motivational circuits" - neuronal nuclei involved in the assessment of stimulus salience and cognitive-emotional integration.

Mu Opioid Receptor-Mediated Neurotransmission



From Zubieta JK

Ms. B reveals sexual trauma

- During a session on pain coping with MSW, Ms. B speaks of nightmares of molestation
- She says her grandfather used to visit her room at night when stayed with them
- This occurred age 7-13 until he died
- She tried to tell her mother, but she said that "Grandpa wouldn't do such a thing."
- Ms. B also reports she drank heavily and took "pain pills" until she left her first husband

Ms. B reveals sexual trauma

- Ms. B's trauma history now includes the essential elements of helplessness and loneliness (Bergman)
- Survival requires dissociation from the self that has been overwhelmed and destroyed
- Repeat trauma breaks through dissociation once again making Ms. B helpless and alone
- So she turns to opioids

Opioids as stress modulators

- Targeted rejection events (e.g., fired, broken up)
  - assoc. with 22x increase in depression
  - With rejection, MDE patients show MOR deactivation but controls show MOR activation in amygdala
  - These social rejections are a threat to physical survival for intensely social primates
- SNP in OPRM1 increases sensitivity to both physical pain and social rejection
  - G allele carriers need more opioids after surgery, tend to fearful adult attachment

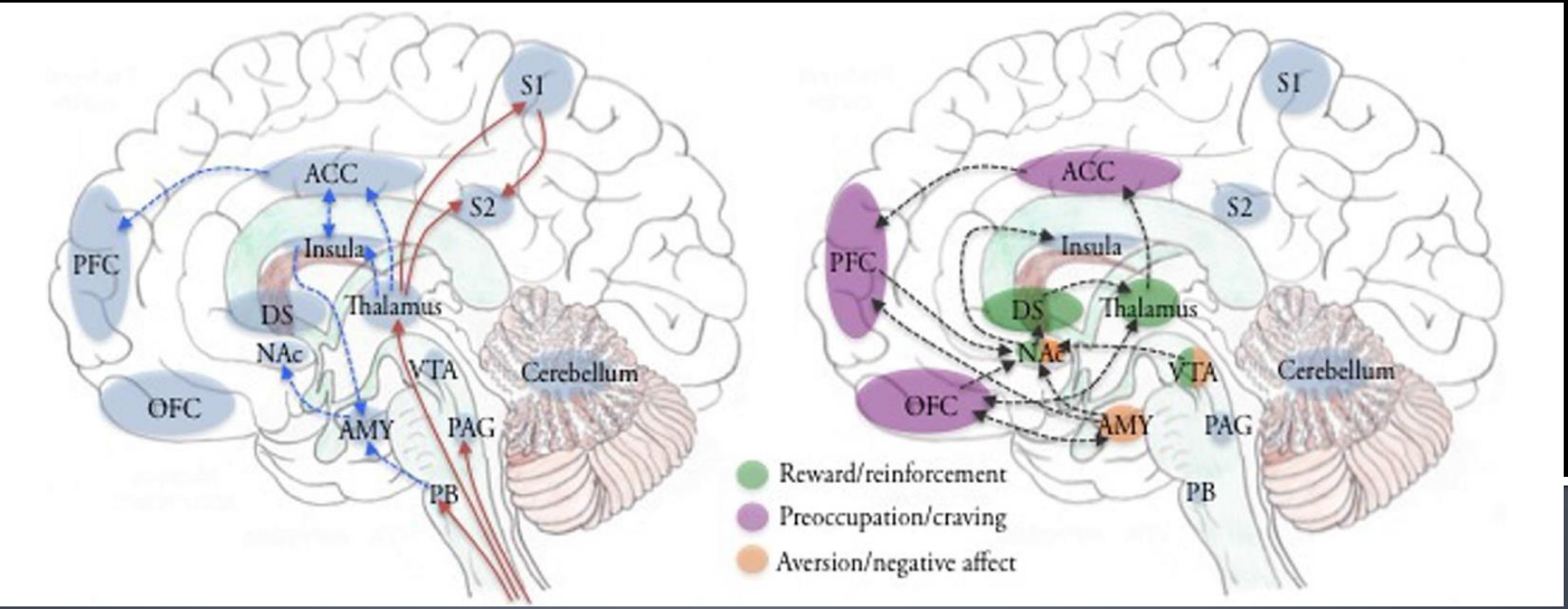
Opioids vs steroids in the CNS

- CRF coordinates autonomic, behavioral, and cognitive response to stress w endocrine syst.
- In acute stress, CRF acts on LC to increase arousal, attention, behavioral flexibility
- EOS has opposite effect on LC, helps neurons and organism recover after stressor is gone
- With chronic stress (PTSD), opioid tolerance and dependence may develop w/o meds

Rethinking the nature of pain

- Neuroscience suggests that human pain is a survival-oriented behavioral drive rather than an injury-caused aversive sensation
- EOS continuously modulates the transmission of nociception to promote survival
- Brain encodes pain salience, not pain intensity determined by survival-relevant context
- Pain system is a danger-detection system rather than a damage-detection system (Moseley)

CNS opioid and dopamine systems integrate pain with reward system



From Cahill et al, 2014

Brain's opioid and dopamine systems

- DA: in reward-driven actions-- "wanting"
  Opioids: in hedonic tone– "liking"
- These systems are integrated to modulate the valence (positive/negative) and salience (strong/weak) of pain
- DA encodes motivational salience of pain
  - whether pain should be endured for rewards
  - when pain has positive valence or low salience

Chronic pain as reward deficiency

- Chronic pain disrupts hedonic homeostasis, increasing relevance and reward of pain relief (Elman and Borsook)
- As persistent stress, chronic pain increases endogenous opioid tone, but decreases phasic changes in endogenous opioids in response to transient stressors.
- Similarly, exogenous opioid therapy initially induces pain relief, but then induces tolerance (to pain relief and mood elevation) and dependence (a need for opioids to avoid pain and distress).

Ms. B got relief from opioids

- Oxycodone provided relief of pain, insomnia, anxiety, agitation and anger
- But Ms. B kept needing more oxycodone, developing tolerance and dependence

- Opioids reduce hyperarousal, re-experiencing but deepen numbing and avoidance
- This leads to PTSD perpetuations

Ms B has opioid dependence

- Opioid-induced syndromes:
  - Hypogonadism: absent libido, amenorrhea, due to suppression of gonadotropins (Gudin 2015)
  - Opioid-induced hyperalgesia (OIH): escalating generalized pain and allodynia despite high-dose opioid therapy (Roeckel 2016)
  - Opioid immunosuppression (Plein 2018)
    - Opioids suppress adaptive and innate immune systems
    - Increased risk of pneumonia (Dublin 2011)

Ms. B has opioid dependence

- Anhedonia- reward deficiency:
  - insensitivity to rewards beyond opioids/pain relief
  - Continual crisis orientation with forgetting of personal values: "life orientation system"
- Social cognitive impairment:
  - tapered patients no longer feel like a "zombie"
  - Spouses confirm return to pre-opioid personality
  - Impaired emotion perception and social inference in opioid maintenance patients (McDonald 2013)

Opioids produce the illusion of complete safety

"Doing heroin is like being hugged by God…"
--Heroin addict

Quoted in *Addiction and Responsibility* by Francis Seeburger

Substances vs relationships

- As substance use deepens, relationships deteriorate
  - Does not require development full addiction, dependence may be enough
  - Opioids: "like being hugged by God"
- If substances are to be reduced, relationships must be recovered
  - Reach for the phone rather than pill bottle
  - But complicated restoration process in those with early, multiple or severe trauma

Opioid therapy: pain relief or addiction?

- We can now understand that this standard framing of opioid policy is too simple and ignores what we have reviewed about EOS
- Many neuroadaptations and harms assoc. w continuous opioid therapy arise with the state of dependence, do not require addiction
  - Mass exposure only w ER/LA opioids since 1990's
  - High-dose patients may not be able to DC

Ms. B: opioids to relationships

- Ms. B attempted opioid taper, but became too anxious, angry and overwhelmed
  - Opioids simulated safety too well
- She transitioned onto SL buprenorphine with improvement in her pain and anxiety
- Currently engaged in Cognitive Processing Therapy to address her PTSD and trauma
- Hopes to taper off opioids in the future

Human pain: between suffering and survival

- Human pain exists to promote both physical and psychological survival.
- Mammalian social pain system piggybacked onto physical pain system of non-mammals.
- EOS (+steroid, +dopamine) modulates the pain of both broken arms and broken hearts to promote species survival
- Exogenous opioids disrupt opioid stress-modulation, producing opioid dependence